TREATMENT OF LEPROSY IN THE UNITED STATES*

WILLIAM R. LEVIS, M.D.
Director, New York City—Region II
Hansen's Disease Program

Review of definitive articles on the recommended chemotherapy of leprosy in the United States shows a significant change in approach and philosophy from 1965[1] to 1976[2] to 1982[3]. American recommendations also differ significantly from the recent guidelines recommended by the World Health Organization (W.H.O.).[4] The underlying rationale behind both the American and W.H.O. recommendations is combination or multidrug therapy to combat the emergence of drug resistance.[5] Drug resistance has increased significantly during the past decade, and may prove more formidable than is currently apparent. *Mycobacterium leprae,* the causative organism of leprosy, has still not been reproducibly grown on artificial media. As a result, the principles of diagnosis and methods for following the effects of treatment are still cumbersome. Hemotoxylin and eosin tissue sections, slit smears, and histochemistry with the Fite stain are used for diagnosis and to assess the number of acid fast bacilli which are intact (morphologic index) and the total number of bacilli per field (bacterial index). A morphologic index greater than 0 or a stable or rising bacterial index (1^+ to 6^+) may be the first indications of drug resistance. Both indices require some degree of histopathologic expertise, and the bacterial index varies significantly from one area to another.

IMMUNODIAGNOSTIC TESTING AND THE CLINICAL CLASSIFICATION OF LEPROSY

Leprosy is a chronic infection predominately of the skin and peripheral

*Presented as part of a *Symposium on Hansen's Disease* sponsored by the Committee on Public Health and the New York City Department of Health and held at the New York Academy of Medicine October 5, 1983.

Address for reprint requests: Director, New York City-Region II Hansen's Disease Program, Bayley Seton Hospital, Staten Island, N.Y. 10304

nerves. Hepatosplenomegaly, lymphadenopathy, ocular, testicular, renal, thyroid, parathyroid, laryngeal or other mucous membrane involvement also occur. Leprosy has a well developed clinical classification introduced by the British leprologists Ridley and Jopling.[6] This intricate disease classification is extremely useful and should be employed in other inflammatory and even neoplastic disorders. Basically, the classification represents an immunologic spectrum from high immune response (tuberculoid) to low immune response (lepromatous). Most leprologists employ a variation of the Ridley-Jopling schema and can reasonably communicate the type of patient involved. There is room for subclassification of the original five groups, which include polar tuberculoid, borderline tuberculoid, mid-borderline, borderline lepromatous, and polar lepromatous. Our program employs a neuroimmunologic classification of leprosy based on the histopathologic criteria of Ridley and Jopling[7] and C. K. Job,[8] clinical extent of the disease, degree and type of neuropathy, and immunodiagnostic testing (see below). Thus, localized borderline tuberculoid disease without significant peripheral nerve damage represents a low risk residual deformity patient compared to a disseminated borderline tuberculoid patient with severe peripheral neuropathy of all four extremities (disseminated borderline tuberculoid 4+). Additional understanding of the cellular immune system has provided further insight into the immunologic spectrum and pathogenesis of leprosy infections. Major understanding stems from observation of the increasingly lower degree of *in vitro* lymphocyte transformation to *M. leprae* as one moves toward the lepromatous pole.[9] This decreasing immunologic responsiveness is paralleled by a diminished number and proportion of helper thymus derived (T) lymphocytes in the skin infiltrates of leprosy patients as identified by monoclonal reagents (OKT_4 and leu *3*).[10] Immunopathologic study with monoclonal reagents and *in vitro* functional studies of lymphocyte function,[9] including suppressor cell assays,[11] provide an immunodiagnostic basis for the clinical classification of leprosy. Additional clinical information for the immune classification, and possible disease activity information, is available by study of the humoral immune system.[12] Increases in serum IgG and IgM become more pronounced toward the lepromatous end of the spectrum. In recent years several groups have reported on specific antibodies to *M. leprae* armadillo derived phenolic glycolipids.[13-16] There are some discrepancies as to the

degree of IgG versus IgM phenolic glycolipid antibodies and whether or not IgG or IgM phenolic glycolipid antibodies paralleled the extent of the leprosy infection in multibacillary patients. Nevertheless, once some of the technical aspects of specific antibody detection, reagent and possible substrate variations are developed, phenolic glycolipids antibodies should provide a very useful addition to the bacillary index for following disease activity. Whether this approach will also, under other conditions, provide a serologic screening method for leprosy infection requires further study. In summary, a combination of cellular and humoral immune studies is extremely useful in classifying both the type and extent of leprosy infection. Further developments in immunodiagnostics may also provide a rational approach to immunotherapy of leprosy.

Drug Resistance

Current problems of drug screening and chemotherapeutic efficacy in leprosy have been well discussed by Levy,[17] who points out that significant advances, including the mouse foot pad assay,[18] have taken place over the past two decades, but emphasizes the limitations and even imprecision of available technology for both drug screening and evaluation of chemotherapeutic efficacy. W.H.O. has recognized that the emergence of significant drug resistance requires multidrug treatment of leprosy.[4] However, current American recommendations as outlined by Jacobsen[3] differ significantly from the W.H.O. recommendations. There are several reasons for these differences. W.H.O. recommendations make several compromises, realizing that rifampin is a costly drug, and made daily clofazimine the principal drug to combat dapsone resistant cases. Once monthly rifampin is undoubtedly undertreatment and does not take advantage of the highly cidal action of this antibiotic.[19-21] Thus, American recommendations include rifampin in a "full" dosage of 600 mg daily in combination with dapsone at 100 mg daily. This two drug combination can be criticized because of the rising number of dapsone resistant cases. Dapsone resistant cases would then be under treatment with only one effective drug, namely, rifampin. This treatment would, at least theoretically by analogy to the proven requirement for multidrug therapy in tuberculosis, lead to further rifampin resistance. However, because patients in the urban United States so often refuse clofazimine, this dual therapy is currently utilized in conjunction with a mouse foot pad

antibiotic sensitivity test on all multibacillary cases. If results indicate dapsone resistance, clofazimine must then be instituted. As is often the case, a patient may already have received antibiotic therapy without a mouse foot pad test, which takes six to 12 months. In such cases it is wise to discuss the risk-benefit ratio and degree of discoloration due to clofazimine. Ethionamide may provide an additional alternative, but the combination of rifampin and ethionamide should be avoided because of hepatotoxicity. At present, it is difficult to produce precise statistics on drug resistance patterns from different areas of the world. However, drug resistance to dapsone should be considered established everywhere, even though mouse foot pad statistics may be lacking. The current percentage of resistant cases varies from one area to another, but any percentage requires a multidrug treatment program. Furthermore, rifampin resistance, while currently less common than dapsone resistance, may already be increasing. While clofazimine resistance is currently almost nonexistent, it would be almost too fortuitous to expect that we have inherited a drug to which *M. leprae* will not mutate. At the present time there are many uncertainties. There are no readily available methods to measure mutation rates to *M. leprae,* but analogy to other bacteria suggests that a rate exists for each antibiotic. The time between introduction of a drug to the development of secondary resistance may be related to this unknown mutation rate along with other such variables as dosage, compliance, and genetic factors. The time lag between the emergence of secondary and primary (see appendix) resistance is probably mostly a reflection of the incubation period of the disease, which is a minimum of three to five years, and may be as long as 20 or more years.[22,23]. Thus, because leprosy is a slow disease to develop and slow to respond, it is comparatively early in the antibiotic era. An increase in both rifampin and clofazimine resistance can be anticipated unless the unknown mutation rates turn out to be low. It is also possible that effective multidrug treatment will diminish future emergence of drug resistant organisms.

Corticosteroids and Thalidomide in the Treatment of Leprosy Reactions

Judicious use of corticosteroids is required to treat the reactions of leprosy.[25] These reactions include erythema nodosum leprosum, acute and chronic inflammatory neuropathies and neuritis, reversal and down-

grading reactions, and mixed or combinations of the above reactions. The decision on the dosage and duration of corticosteroids and thalidomide, alone or in combination, depends on the severity and type of reaction, the type of patient (borderline or midborderline tuberculoid, borderline or polar lepromatous), male or female, degree of neuropathy, the risk-benefit ratio of longer term use of corticosteroids, the initial response to therapy, and the presence or absence of relative contraindications to the use of corticosteroids, (e.g., peptic ulcer disease, hypertension, active or inactive tuberculosis, diabetes).

Example 1. Probable pure erythema nodosum leprosum with and without neuropathy. The diagnosis of pure erythema nodosum leprosum is made by knowing the patient is multibacillary (borderline, subpolar, or polar lepromatous), the presence of panniculitis (subcutaneous erythematous nodules), the presence of arthritis or arthralgias, fever, leukocytosis, and an increase in urinary sediment (protein, leukocytes, erythrocytes). When such a patient is male or female of nonchildbearing potential, the erythema nodosum leprosum can be treated with thalidomide beginning at 100 mg four times a day or three times a day depending on the patient's weight and severity of the reaction, and should respond to thalidomide within a few days. Patients should be followed for defervescence, decrease in leukocytosis, clearing of urinary sediment, improvement of arthralgias, improvement of skin lesions, and a general feeling of well being. Should any or all of these signs and symptoms persist even with continuous thalidomide, corticosteroids should then be administered. The duration of the thalidomide trial depends on the degree of unresponsiveness and the presence or absence of inflammatory neuropathy or active neuritis. Whether there is true thalidomide refractory erythema nodosum leprosum or whether the reaction is of a mixed type is not always easy to determine. At present there are no reproducible clinically available laboratory tests reliably able to distinguish pure erythema nodosum leprosum from erythema nodosum leprosum with reversal and/or downgrading reactions. Serum IgM levels,[24] immune complexes, CH50 levels are worth obtaining, but at present further studies are required before they become clinically useful. A reversal reaction or T cell component should be suspected when thalidomide unresponsiveness is found. Additional clinical signs of reversal reactions include cutaneous flaring limited to existing lesions, lymphocytosis rather than polymorphonuclear leukocytosis, and usually a more symmetrical neuropathy

than that which occurs with erythema nodosum leprosum. However, in the presence of erythema nodosum leprosum these clinical signs are not highly reliable, and management of the reactional status should progress to corticosteroids when refractoriness to thalidomide is encountered. A major guide in treatment of leprosy is preservation of as much peripheral nerve function as possible to avoid the problems of residual deformity and anesthetic extremities. Because corticosteroids have an important role in achieving this end, it is important that the leprologist be well schooled in the principles and hazards of corticosteroid therapy.

Once the decision to institute corticosteroids is determined, it is important to begin with a high enough dose. This means steroids daily or four times a day. Prednisone at a dose of 60 mg every morning should be considered a minimum starting dose in the treatment of erythema nodosum leprosum, especially when active neuropathy is present. Lower doses may well suppress the panniculitis, arthralgias, fever, and leukocytosis, only to allow progressive nerve damage. Often 60 mg every day is inadequate as a starting dose. Since it is important to begin on top of the inflammatory process, a starting dose of 80, 100, or 120 mg of prednisone should be employed when faced with "major" erythema nodosum leprosum symptoms such as fever greater than 103°F, intractable arthritis or arthralgias, leukocytosis over 20,000/mm^3 or large areas of panniculitis—greater than 3 cm of induration. In acute major erythema nodosum leprosum, it is best to begin with divided doses of prednisone 20 to 30 mg four times a day. After one week the reaction is almost always under control (occasional patients may require in excess of 120 mg of prednisone. Once the reaction is controlled for a week, very slow tapering of prednisone should take place to avoid exacerbation. When the reaction has been controlled by prednisone divided into four daily doses, the first step in tapering should be to a one time every morning dosage at the same total daily dose. A reduction from 20 mg four times a day to 80 mg every morning is a sizeable reduction in anti-inflammatory therapy. This adjustment can usually be made when erythema nodosum leprosum is under control, but periods of twice a day and even three times a day scheduling intervals may be required before moving to every morning doses in fulminant cases. Once the controlled patient gets prednisone every morning, the dosage should be continued another week before tapering further. At this point tapering should be very slow, 2.5 mg every other day. Thus, over a period of weeks the patient can be

adjusted from 60 mg every morning to 60; 57.5; 60; 55 and so on until at 60 mg and 10 mg on alternate days. Since 10 mg is still above the average daily physiologic equivalent of 5 to 7.5 mg, it is safe to taper any patient to this level. When tapering, the patient should be held at a given dose should a recurrence occur before further tapering. In patients who can be tapered to 60 mg and 10 mg of prednisone on alternate days without any flare, the decision to go to alternate day therapy is the next to be made. The decision on how to go to alternate day therapy depends on the prior duration of corticosteroid therapy and whether or not the patient is at risk for adrenal suppression and/or adrenal insufficiency (for more detailed discussion of the hypothalmic-pituitary-adrenal axis the reader is referred to references 25 and 26).

In treatment of acute erythema nodosum leprosum or reversal reactions (see below), the slow tapering to alternate day corticosteroid therapy can be achieved without complications. In patients treated with daily corticosteroids for more than a few months, the danger of adrenal insufficiency needs to be considered. Generally, by keeping the patient on 60 mg every other day and tapering the alternate day from 10 mg very slowly, one can avoid the symptoms of adrenal insufficiency. Thus, maintenance of a patient on 60 mg every other day and 5 mg every other day for several weeks, followed by 60 mg and 2.5 mg every other day for several weeks before going to 60 mg and 0 mg every other day will allow the transition to alternate day therapy. Once the patient is maintained on alternate day therapy, plasma cortisol levels should be determined. When erythema nodosum leprosum is still under control, slow tapering can again be initiated. Blood pressure monitoring, assessment of alternate day moods, nonspecific headache and myalgia-like symptoms should be monitored along with plasma cortisol levels. By using these principles of rapid initiation of daily corticosteroids and slow tapering to an alternate day regimen, adrenal insufficiency can be avoided in the vast majority of premenopausal women in whom thalidomide is contraindicated. However, management of premenopausal women with chronic erythema nodosum leprosum is still a significant problem in the treatment of leprosy. As discussed below, clofazimine is helpful for these patients, but ambulatory patients may either refuse or be noncompliant. Nonsteroidal anti-inflammatory agents need to be further investigated for use in erythema nodosum leprosum.

Example 2. Probable pure reversal reaction. The diagnosis of pure

reversal reaction is made in a patient whose classification falls anywhere from borderline tuberculoid to subpolar lepromatous. It is generally stated that polar lepromatous cases remain polar and do not upgrade or undergo a reversal reaction. Exceptions, of course, do occur in which lepromatous patients do upgrade. At present, precise testing is not available to establish which patients may develop some cell-mediated immune competence to *M. leprae* and subsequently upgrade. Thus, it is important to suspect a component of a reversal reaction in any patient in reaction who fails to respond to thalidomide or any patient with a sudden onset of symmetrical peripheral neuropathy. The treatment for pure reversal reaction is corticosteroids; there is no significant response to thalidomide. A general rule is that more acute and fulminant reversal reactions occur in paucibacillary disease. If a borderline tuberculoid patient goes into reaction, it is most likely to be a pure reversal reaction (downgrading with and without concomitant erythema nodosum leprosum being the principal differential). Clinically, skin lesions may flare, with the flare limited to the lesions and skin around the lesions, along with sudden onset of parasthesias and sensation loss. In borderline tuberculoid disease, prompt initiation of prednisone at 60 to 80 mg every day is important to avoid irreversible damage to the nerves. Even in cases where the flare appears to be predominately in the skin, if the patient is borderline tuberculoid, corticosteroids should be initiated. In borderline or subpolar lepromatous patients, the reversal reaction tends to be more chronic and indolent—thus, if the reaction appears limited to skin, corticosteroids can be temporarily withheld—although careful attention need be paid to such patients to detect nerve involvement. The duration and dosage of corticosteroid needs to be individualized to the patient. Borderline tuberculoid patients generally require a shorter course than borderline lepromatous patients. Once nerve reactions are controlled with daily prednisone, the gradual transition to an alternate day regimen will often maintain control. Clofazimine therapy may facilitate early withdrawal of corticosteroid therapy. The major reason to use corticosteroids is to avoid permanent nerve damage. Thus, parasthesias or peripheral sensation improvement or loss are the main clinical symptoms and signs used to adjust corticosteroid scheduling. Electrophysiologic monitoring of the nerves may prove useful in the future. However, several problems still remain before precise quantitative sequential electrophysiologic monitoring becomes feasible.

Example 3. Mixed reactions. Such reactions are neither pure erythema

nodosum leprosum nor pure reversal. They occur in borderline and midborderline tuberculoid, borderline and subpolar lepromatous patients. A borderline tuberculoid patient can downgrade to midborderline or borderline lepromatous and, in the process, develop erythema nodosum leprosum in addition to a subsequent reversal reaction, i.e., the patient is unstable. Corticosteroids are the treatment of choice using the principles outlined under examples 1 and 2 above. Thalidomide will assist the erythema nodosum leprosum component of such reactions and may reduce the dose of corticosteroids required to control the reactions. In the case of a borderline or subpolar lepromatous patient, it is possible first to give a trial of thalidomide to determine the extent of thalidomide responsiveness and/or extent of erythema nodosum leprosum. The neuropathy must be given consideration in determining the duration and dosage of corticosteroids.

Role of B663-clofazimine for reactions. Clofazimine is useful in the treatment of reactions,[30] but only on a chronic basis, not for acute control. It is particularly useful in premenopausal women with chronic erythema nodosum leprosum, and will reduce the dosage of corticosteroids required for control. Initially, a dosage as high as 300 mg per day is advocated, but this can be tapered to 100 mg every day or even 100 mg three times a week. W.H.O. guidelines recommend 50 mg clofazimine daily as antibacterial combination therapy.[4] The two main problems with clofazimine are discoloration due to analine dye tissue deposition and abdominal pain and gastrointestinal symptoms secondary to deposits in the gastrointestinal tract. Because clofazimine is preferentially engulfed by macrophages, the degree of disfigurement is less in patients with lower activity and therefore fewer macrophages. Thus, if multibacillary leprosy is first controlled using a combination of dapsone and rifampin, along with control of reactions using thalidomide and corticosteroids, the use of clofazimine can be kept to a minimum. However, clofazimine needs to be used in cases of either dapsone or rifampin resistance. Clofazimine must also be initiated in patients unable to tolerate either dapsone (allergy to dapsone, G6PD deficiency, leukopenia, thrombocytopenia, or anemia contributed to by dapsone) or rifampin (most commonly hepatotoxicity, HB antigen positivity, occasional allergy).

Thalidomide. Thalidomide (α-N-phthalimidoglutarimide) is the treatment of choice for all patients with erythema nodosum leprosum who are eligible. Because of its well known teratogenic effects, current United

States investigational new drug guidelines prohibit the use of thalidomide in women of childbearing potential. Some women with chronic erythema nodosum leprosum electively undergo tubal ligation to receive thalidomide. Sheskin[28,29] initially reported the beneficial effects of thalidomide, and many subsequent trials, including a W.H.O. double blind trial,[30] have confirmed a high degree of responsiveness of pure erythema nodosum leprosum. Other conditions,[31] particularly inflammatory conditions, may be affected by thalidomide, but none has been as extensively studied as erythema nodosum leprosum. Impressive results have been reported in actinic prurigo,[32] an inflammatory photosensitive disorder best described among Indians of North and South America. Impressive results with thalidomide have also been reported in the treatment of discoid lupus erythematosus.[33] Additional reports in a variety of conditions including Behcets' syndome, pyoderma gangrenosum, Weber-Christian disease, postherpetic neuralagia, and others[31] require further evaluation. Reports of significant neuropathy in discoid lupus erythematosus patients,[33] as well as thalidomide induced experimental neuropathy, along with the teratogenic effects require judicious and careful use of this drug for other conditions. The degree of neuropathy related to thalidomide in multibacillary leprosy is under continued monitoring. The investigational new drug protocol calls for frequent tapering and total cessation of thalidomide therapy when possible. Most erythema nodosum leprosum can be rapidly controlled in two to four days using thalidomide. Cases refractory to rapid control may in some instances be mixed reactions, as discussed above. Factors that lead to a lack of responsiveness of pure erythema nodosum leprosum are still poorly identified. Prior treatment with corticosteroids may be one such factor leading to thalidomide refractory erythema, although this is not currently well documented. Other than teratogenicity and some neuropathy, other side effects have been minimal. Drowsiness, occasional peripheral edema, and occasional eosinophilia can occur.

Duration of Antibiotic Therapy and Maintenance Regimes

Multidrug therapy is relatively new in the treatment of leprosy, and methods to quantify the therapeutic response are still relatively imprecise. Clinical response and bacterial index of multibacillary cases are measured in months or even in years. As a result, no clear drug trial data support

the precise duration of multidrug therapy versus a single drug "maintenance" program. The concept of multidrug therapy evolved from tuberculosis data. No direct supportive data yet indicate a requirement for this approach if the *M. leprae* are known to be sensitive. However, since drug resistance is now well recognized, some theoretical recommendations can be made. Current recommendations will undoubtedly change as disease patterns evolve. If current multidrug therapy is widely used and compliance rates maintained, it is possible that a beneficial effect will be detected by a decreasing incidence of leprosy in areas where effective chemotherapy programs are instituted. Even a decrease in the incidence of drug resistance may occur, as carefully monitored tuberculosis chemotherapy multidrug treatment has been reported to reduce drug resistance. Alternatively, because of a limited number of known effective drugs and a lag phase before the appearance of both primary and secondary resistance, an increase of drug resistant leprosy is equally possible. A major drawback to chemotherapeutic impact at the public health level is the long period of therapy required for multibacillary cases, a factor which may prove more formidable than in tuberculosis for controlling resistance. There is also a lack of effective long-term parenteral medication. Jacobson recommended at least two years of combination chemotherapy for multibacillary cases followed by dapsone monotherapy for life.[3] In known drug resistant cases, combination therapy is followed by monotherapy with clofazimine, rifampin, or ethionamide. At this time, these figures should be taken as minimal duration for multidrug treatment under ideal circumstances. In patients who show a significant decrease in the bacterial index, multidrug therapy may be stopped as early as after two years of combination therapy. Maintenance dapsone can be used when mouse foot pad test results indicate sensitivity. On the other hand, ambulatory care patients are probably not as compliant with daily medications as patients in a leprosarium. It is difficult to stop multidrug therapy on a patient with a significant bacterial index, particularly if mouse foot pad results are not available. At this time, the decision of when to go to a single drug maintenance program needs to be individualized, taking into account the bacterial index, mouse foot pad results, and any evidence of untoward effects of individual drugs. All patients getting continuous daily rifampin need liver function tests at three month intervals, or more frequently if any elevation of the alkaline phosphatase, SGOT or SGPT are noted.

Transient elevations of any of these will often disappear at a lower dose of rifampin such as 300 mg every day. An elevation of serum bilirubin is an indication to stop rifampin. Elevations of liver enzymes will depend on the sensitivity of individual laboratories.

In summary, at this time it is difficult to recommend a precise duration for multidrug therapy of multibacillary cases. While tuberculosis therapy has well defined and documented clinical trial data to support treatment durations as short as nine months, this is not the case in leprosy. Leprosy tends to be recidivistic. Problems of neural persistence,[34] bacillary persistence in general,[35] and drug resistance require that the duration of therapy be individualized. At this time, all multibacillary patients require lifetime monitoring for recurrence.

This review has not dealt with duration of therapy for paucibacillary leprosy. Compliant patients who respond to combined dapsone and refampin may have recrudescence when rifampin is discontinued after six months. Because clinical response is the only currently available method to suspect drug resistant paucibacillary disease, combined therapy for a short duration of six months followed by dapsone monotherapy is recommended. Clofazimine can be used for paucibacillary disease when rifampin is contraindicated. Borderline tuberculoid leprosy can be destructive disease, and borderline tuberculoid patients who have peripheral nerve destruction can become difficult residual deformity patients. In contrast, multibacillary patients who have managed to remain free of significant neural damage can have very little or no residual deformity. Dapsone monotherapy may be adequate for patients with localized paucibacillary disease, but such patients should be watched for evidence of dissemination or progression.

Leprosy Control: Contact Examinations, Chemoprophylaxis and Immunoprophylaxis

At this particular time, leprosy control recommendations of the National Hansen's Disease Program include examination of household contacts and first or second degree relations. A screening contact examination should emphasize neurologic symptoms—numbness, tingling, parasthesias of any kind and skin lesions, duration and type, evidence of madaurosis. Nerve palpation, peripheral neurologic examination, rheumatic symptoms and a family history for leprosy, autoimmune disorders, or skin disease of any

kind should also be included in a screening contact examination. Skin biopsy, slit smears, and nerve conduction velocities are obtained in contacts with suggestive signs or symptoms. Filice et al.[36] of the Center for Disease Control have recommended three years of full dose dapsone therapy for household contacts of multibacillary patients. Such prophylactic dapsone may decrease the incidence of leprosy in compliant contacts, but it is difficult to maintain compliance in an otherwise healthy ambulatory population, and sporadic use of dapsone could theoretically predispose to drug resistance. Thus, while chemoprophylaxis may prove useful, it should not be initiated in place of periodic contact examinations.

Immunoprophylaxis for leprosy is only in a formative stage. At this point there is no recommended leprosy vaccine. One trial in Uganda showed up to 80% protection with Bacillus of Calmette and Guerin (BCG).[37] A trial with the same BCG strain in Burma showed no protective effect except for a possible significant effect in children under three years of age.[38] Convit and coworkers[39] have reported an immunotherapeutic effect of a combination of armadillo-derived *M. leprae* and BCG. A similar combination of *M. leprae* and BCG are scheduled for W.H.O. immunoprophylactic field trials. These trials are in the early formative stages and even the dose of administration has not yet been determined. Significant theoretical consideration has been given to whether or not an immunoprophylactic approach could work.[40] Shepard has shown a lack of effect of BCG and *M. leprae* in tolerized mice.[41]

Summary

Current recommendations for treatment of leprosy in the United States differ from World Health Organization guidelines. Daily rifampin and dapsone in combination are recommended in the United States, and mouse foot pad antibiotic sensitivity testing should be routinely obtained on all multibacillary cases when possible. Clofazimine is used in reactional premenopausal women, drug resistant patients, and patients for whom either rifampin or dapsone are contraindicated. The emergence of increasing drug resistance requires multidrug antibiotic therapy. Drug resistance is the underlying factor behind both the American and W.H.O. recommendations. There is a need for new antibiotics in the treatment of leprosy as well as improved methods of screening and monitoring. Current recommendations for multidrug therapy may provide effective control of leprosy. Alternatively, dapsone resistance may continue to increase.

Secondary resistance followed by primary resistance to other antileprosy antibiotics may also develop, as it has for dapsone. Despite the limited number of effective antibiotics and emerging drug resistance at the present time, it is possible effectively to treat most patients with leprosy to the point that they can lead productive lives in an ambulatory care setting. While the duration of therapy, coexistent social problems, variable degrees of disability, and associated medical problems will challenge health care personnel, results are unusually rewarding for both the patients and the health care team.

Appendix

Resistance to dapsone is referred to as "secondary" when it develops in a patient where the *M. leprae* are initially sensitive. When resistance to dapsone is noted from the onset of infection, it is referred to as "primary" resistance. Secondary resistance appears to occur only after 10 to 14 years of treatment with dapsone monotherapy. Presumably, such resistance occurs as a result of selecting *M. leprae* dapsone resistant mutants. Primary resistance would result from patients who have developed secondary resistance with subsequent transmission. Available data are compatible with this premise (including the time lag from introducing dapsone to secondary and primary antibiotic resistant mutants). Thus, a significant length of time appears to be required from the introduction of an antibiotic in the treatment of leprosy to the development of drug resistant mutants. The time lags would include the 10 to 15 years required for secondary resistance to develop, plus the minimum three to five years (and possibly up to 20 or more years) incubation period before the emergence of primary resistant cases. There may be a direct relationship between drug resistant mutation rates and the time of appearance of drug resistance cases. Drug resistant cases would show up earlier with high mutation rates. Mutation rates cannot be easily measured in a noncultivatable mycobacterium. The methods for detecting drug resistance are also difficult. Existing facts indicate a rise in drug resistance patterns to all antibiotics unless the tide is turned by current and future therapeutic developments.

Acknowledgements

A special thanks to Joseph Bermudez, Director, Social Services, and to the excellent physical therapy staff at Bayley Seton Hospital.

REFERENCES

1. Trautman, J. R.: The management of leprosy and its complications. *N. Engl. J. Med. 273:*756-58, 1965.
2. Jacobson, R. R. and Trautman, J. R.: The diagnosis and treatment of leprosy. *South. Med. J. 69:*1-7, 1976.
3. Jacobson, R. R.: The treatment of leprosy (Hansen's disease). *Hosp. Form. 17:*1076-91, 1982.
4. World Health Organization: *Chemotherapy of Leprosy for Control Programmes.* WHO Technical Report Series No. 675, Publ. No. 15BN 92 4 120675 6. Geneva, World Health Organization, 1982.
5. Increase in prevalence of leprosy caused by dapone-resistant *Mycobacterium leprae. Morb. Mort. Weekly Rep. 30:*637-38, 1982.
6. Ridley, D. S. and Jopling, W. H.: A classification of leprosy for research purposes. *Lepr. Rev. 33:*119-28, 1962.
7. Ridley, D. S. and Jopling, W. H.: Classification of leprosy according to immunity: A five group system. *Int. J. Lepr. 34:*255-73, 1966.
8. Job, C. K.: The immunological spectrum in leprosy and its significance. *Indian J. Pathol. Bacteriol. 17:*75-78, 1974.
9. Godal, T.: Immunological aspects of leprosy—present status. *Prog. Allergy 25:*211-42, 1978.
10. Van Voorhis, W. C., Kaplan, G., Sarno, E. N., et al.: The cutaneous infiltrates of leprosy. Cellular characteristics and the predominant T-cell phenotype. *N. Engl. J. Med. 307:*1593-97, 1982.
11. Mehra, V., Convit, J., Rubinstein, A., and Bloom, B.: Activated suppressor T-cells in leprosy. *J. Immunol. 129:*1946-51, 1983.
12. Melsom, R.: Serodiagnosis of leprosy: The past, the present, and some prospects for the future. *Int. J. Lepr. 51:*235-52, 1983.
13. Hunter, S. and Brennan, P.: A novel phenolic glycolipid from *Mycobacterium leprae* possibly involved in immunogenicity and pathogenicity. *J. Bact. 147:*728, 1981.
14. Brett, S. J., Draper, P., Payne, S., et al.: Serological activity of a characteristic phenolic glycolipid from *Mycobacterium leprae* in sera from patients with leprosy and tuberculosis. *Immunology 52:*271-79, 1983.
15. Young, D. and Buchanan, T.: A serological test for leprosy with a glycolipid specific for *Mycobacterium leprae. Science 221:*1057-59, 1983.
16. Cho, S., Yanagihara, D. L., Hunter, S. W., et al.: Serological specificity of phenolic glycolipid I from *Mycobacterium leprae* and use in serodiagnosis of leprosy. *Infect. Immun. 41:*1077-83, 1983.
17. Levy, L.: Evolution of the modern chemotherapy of leprosy. *Lepr. Rev. 54:*69-83, 1983.
18. Shepard, C. C.: The experimental disease that follows the injection of human leprosy bacilli into foot pads of mice. *J. Exp. Med. 112:*445-54, 1960.
19. Shepard, C. C., Levy, L., and Fasal, P.: Further experience with the rapid bacteriocidal effect of rifampin on *Mycobacterium leprae. Am. J. Trop. Med. Hyg. 23:*1120-24, 1974.
20. Faber, N. R. and Leiher, D. L.: Evolution of treatment of lepromatous leprosy patients in the Netherlands. *Dermatologica 158:*46-54, 1979.
21. Levy, L., Shepard, C. C., and Fasal, P.: The bactericidal effect of rifampin on *M. leprae* in man a) single doses of 600, 900, and 1200 mg; and b) daily doses of 300 mg. *Int. J. Lepr. 44:*183-87, 1976.
22. Aycock, W. L. and Gordon, J. E.: Leprosy in veterans of American wars. *Am. J. Med. Sci. 214:*329-39, 1947.
23. Levis, W. R., Schuman, J. S., Friedman, S. M., and Newfield, S. A.: An epidemiologic evaluation of leprosy in New York City. *J.A.M.A. 247:*3221-26, 1982.
24. Shannon, E. J., Miranda, R. O., Morales, M., and Hastings, R. C.: Inhibition of de novo IgM antibody synthesis by thalidomide as a relevant mechanism of action in leprosy. *Scand.*

*J. Immunol. 13:*553-62, 1981.
25. Claman, H. N.: Glucocorticosteroids. I: Anti-inflammatory mechanisms. *Hosp. Pract.:* 123-51, 1983.
26. Fauci, A. S.: Corticosteroids in autoimmune disease. *Hosp. Pract.:* 99-114, 1983.
27. Yamachar, S. J. and Vischer, W.: Lamprene (Clofazimine) in leprosy. *Lepr. Rev. 50:* 135-44, 1979.
28. Sheskin, J.: Thalidomide in the treatment of lepra reactions. *Clin. Pharmacol. Ther. 6:*303-06, 1965.
29. Sheskin, J.: Further observations with thalidomide in lepra reactions. *Lepr. Rev. 36:*183-87, 1965.
30. Iyer, C., Languillon, J., Ramuniyam, K., et al.: WHO coordinated short-term double blind trial with thalidomide in the treatment of acute lepra reactions in male lepromatous patients. *Bull. WHO 45:*719-32, 1971.
31. Barnhill, R. L. and McDougall, A. C.: Thalidomide: Use and possible mode of action in reactional lepromatous leprosy and in various other conditions. *J. Am. Acad. Dermatol. 7:*317-23, 1982.
32. Lowel, Hawk, J., Calnan, C., et al.: Thalidomide in actinic prurigo. *J. Dermatol. 108:*467-71, 1983.
33. Knop, J., Bonsmann, G., Happle, R., et al.: Thalidomide in the treatment of sixty cases of chronic discoid lupus erythematosus. *J. Dermatol. 108:*461-66, 1983.
34. Enna, C. D., Jacobsen, R. R., and Mansfield, R. E.: An evaluation of sural nerve biopsy in leprosy. *Int. J. Lepr. 38:*278-81, 1970.
35. Waters, M., Rees, R., and McDougall, A.: Ten years of dapsone in lepromatous leprosy: clinical, bacteriological, and histological assessment and the finding of viable leprosy bacilli. *Lepr. Rev. 45:*288-98, 1974.
36. Filice, G. A. and Fraser, D. W.: Management of household contacts of leprosy patients. *Ann. Int. Med. 88:*538-42, 1978.
37. Kinnear Brown, J. A., Stone, M. M., and Sutherland, I.: BCG vaccination of children against leprosy in Uganda: Results at end of second follow-up. *Br. Med. J. 1:*24-27, 1968.
38. Bechelli, L. M., Barbajasa, P. G., Memgmgyi, K., et al.: BCG vaccination of children against leprosy: Seven year findings of the controlled WHO trial in Burma. *Bull. WHO 48:*325-34, 1973.
39. Convit, J., Aranzayu, N., Zuniga, M., et al.: Immunotherapy and immunoprophylaxis of leprosy. *Lepr. Rev. 54:*47-60, 1983.
40. Godal, T.: The Clayton memorial lecture, 1978: "Is immunoprophylaxis in leprosy feasible?" *Lepr. Rev. 49:*305-17, 1978.
41. Shepard, C. C., Van Landingham, R., Walker, L., et al.: Comparison of the immunogenicity of vaccines prepared from viable *Mycobacterium bouis* BCG, heat-killed *Mycobacterium leprae,* and a mixture of the two for normal *M. leprae*-tolerant mice. *Infect. Immun. 40:*1096-99, 1983.